Editorial

Spironolactone: An Old Friend Rediscovered

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Spironolactone was the first diuretic engineered expressly to block a particular renal transport process: to decrease Na^+ reabsorption within the collecting duct, a primary locus of aldosterone action within the kidney. When spironolactone was originally developed, scientific studies were investigating epithelial ion transport; understanding ion transport was in its formative stages. As a result, spironolactone was initially classified as a K^+-sparing diuretic. Although it technically remains a K^+-sparing diuretic, this functional classification is obsolete, given the growing evidence for aldosterone effects beyond the mediation of ion transport.

DEVELOPMENT

The path to the eventual arrival of spironolactone on the US market was a complicated one, with its release finally occurring at a time when Donald Rumsfeld, the current Secretary of Defense, was chief executive officer of G.D. Searle & Company, the first manufacturer of spironolactone. Spironolactone underwent a succession of approvals, withdrawals, and resubmissions before the 50-mg strength was granted final approval on December 30, 1982. A fixed-dose combination of hydrochlorothiazide and spironolactone (50/50 mg) was also approved on December 30, 1982.[1,2]

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PAST USE

Spironolactone use in the 1970s and 1980s was fairly widespread for the treatment of hypertension, primary aldosteronism, and edematous conditions; i.e., in heart failure (HF), cirrhosis, and nephrotic syndrome. Its K^+-sparing quality also made it an attractive complement to kaliuretic diuretics. There was scant use of spironolactone, however, for therapy-resistant forms of hypertension, even with the shortage of available treatment options.[3] Over time, spironolactone for hypertension was replaced by calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs), which were aggressively marketed.

EARLY DOSING CONSIDERATIONS

What had we learned from the initial treatment experience with spironolactone? Early work by Schrijver and Weinberger[4] in 1979 reported that spironolactone in doses of 200–400 mg/d failed to produce a greater antihypertensive effect than doses of 100 mg/d, and gynecomastia was encountered only at doses of 200–400 mg/d.[4] Schersten et al.[5] also showed that a 200-mg daily dose of spironolactone had a greater antihypertensive effect than a 50-mg dose, but not more than a 100-mg daily dose. Other studies comparing single compared with divided daily doses of 100 mg spironolactone showed that single-dose administration was as effective as a divided dose regimen.[6] These data then served as the basis for the treatment recommendation that patients with essential hypertension receive a daily spironolactone dose of 50–100 mg.

The onset of action for spironolactone was found to be characteristically slow, with a peak response at times of 48 hours or more after the first dose. This response lag likely related to the time needed for the active metabolites of spironolactone to reach steady state plasma/tissue levels.

It was also recognized that spironolactone was effective even when plasma aldosterone values were within the normal range[7] and that it had strong additive effects when given together with drugs such as propranolol,[8] metoprolol,[9] methyldopa,[10] and nifedipine.[11]

What was lacking in the early hypertension treatment experience with spironolactone was its utility in treatment-resistant forms of hypertension. Perhaps the best description of what the future might hold for spironolactone came from Ramsay et al.[3] in 1980. In patients with hypertension resistant to three or four drugs, including a thiazide diuretic, substitution of furosemide for the thiazide, or the addition of spironolactone, brought about significant reductions in blood pressure and body weight. The response did not depend on the presence of overt fluid retention, renal impairment, or the use of antihypertensive drugs of high potency. Women had greater responses than men. Of note, the positive response to spironolactone in this case series was coupled with the correction of presumed plasma volume expansion.[3]

CURRENT DOSING CONSIDERATIONS AND CONTEMPORARY USE

Spironolactone will always remain a compound capable of triggering a prominent natriuretic response when given to patients with cirrhosis/ascites or HF, particularly if combined with a loop and/or a thiazide-type diuretic[12,13]; however, it is not a particularly potent natriuretic agent when acutely administered to hypertensive subjects. It is doubtful that in the foreseeable future spironolactone will be used solely for its diuretic effects.

Spironolactone regresses left ventricular hypertrophy,[14] is antiproteinuric,[15,16] and affords the HF patient survival benefits in excess of what might occur with other HF therapies.[17] These effects are to a degree independent of both BP reduction and volume changes.[15,17] These aspects of spironolactone action are newly characterized and have given a second wind to a compound that was otherwise being ignored. While the cardiology community has openly embraced spironolactone over the past several years, such has not been the case for nephrologists. It can be anticipated that this compound will see expanded use as an antiproteinuric and/or nephroprotective agent.[18]

Where might spironolactone fit in the treatment of hypertension? As previously mentioned, spironolactone has been used for the treatment of hypertension for many years; however, its use in the treatment of resistant hypertension is more recent. It would seem that this is a rational place for the use of this agent. This add-on effect with spironolactone occurs within a matter of weeks, persists for months, and is independent of ethnicity and urinary aldosterone excretion rate.[19] In one study, spironolactone (12.5–50 mg/d) was added to a regimen including a diuretic, an ACE inhibitor, or an ARB. A mean decrease in blood pressure of 21±20 mm Hg/10±14 mm Hg and 25±20 mm Hg/12±12 mm Hg was observed at 6 weeks and 6 months of therapy, respectively.[19] The general benefit of aldosterone receptor antagonists (ARAs) in patients with resistant hypertension suggests that aldosterone may be a more common determinant of resistant hypertension than was first believed.

USAGE CAVEATS

As experience has grown with ARA therapy in resistant hypertension, its side-effect profile has become less obscure. The most common side effect with spironolactone is breast complaints, with approximately 10% of men noting breast tenderness in the studies by Nishizaka et al.[19] In general practice, this number is likely to be higher. Breast symptoms can include an increase in size (occasionally unilateral), the development of nipple and/or breast tenderness, and/or the appearance of discrete breast masses. Gynecomastia generally corrects upon discontinuation of the drug; however, the time required for reversibility can be prolonged, particularly if significant gynecomastia is present. Gynecomastia occurs much less frequently with eplerenone, another ARA, and it can be safely substituted for spironolactone.

Spironolactone use is also associated with a dose-related increase in serum K^+ levels.[20] There are several patient variables that govern the incidence of ARA-related hyperkalemia (the definition of hyperkalemia is variable). The level of renal function is the single most important determinant; thus, patients with underlying renal disease (and, in particular, diabetic renal disease) will be most prone to an increase in serum K^+ values with ARA therapy.[20]

CONCLUSION

Spironolactone has reemerged as an important therapeutic option for the difficult-to-treat hypertensive. It is apparent that aldosterone may be an important contributor to resistant hypertension. The dose for spironolactone in resistant hypertension is in the 25–50-mg range, which is less than generally required for the treatment of primary aldosteronism.[21] Aggressive diuresis should remain the cornerstone of therapy, however, because it noticeably enhances the effect of spironolactone.

Spironolactone use is not without certain drawbacks. The most important downside to spironolactone therapy is the risk of developing clinically relevant hyperkalemia. An appreciation of the risk of the development of hyperkalemia with spironolactone is critical if it is to be used more widely.

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